Remarks

Claims 84, 85, 89-93 and 95-102 are pending in this application. All of the claims stand rejected under 35 U.S.C. § 103. A Final Rejection was issued in this application on March 30, 2001, and an Advisory Action was issued on August 28, 2001. A Request for Continued Examination is being filed concurrently herewith to continue the prosecution of the application.

The outstanding rejection and the amendments to the claims are discussed below. A marked up version of the claim amendments is attached hereto and is entitled "Claim Amendments With Revisions Shown."

I. Claim Amendments.

Independent Claims 84 and 95 have been amended herewith to recite "said composition effective to treat a cancer cell expressing said native cancer antigen." These amendments are supported throughout the specification, which describes reagents and methods for treating cancer with an alphavirus vector expressing a native cancer antigen, *i.e.*, an antigen that is naturally occurring in the cancer cell.

In particular, the present application states at page 17 (lines 9-11): "In a preferred embodiment, alphavirus vectors, preferably VEE vectors, more preferably alphavirus and VEE replicon vectors, can be used to induce an immune response to a specific cancer antigen in cancer patients." The specification further recites at page 17 (lines 18-20): "Thus, alphavirus vectors, preferably VEE vectors, can be used to induce an immune response against a cancer cell antigen which fails to induce an effective immune response, although already present in the cancer cells."

Accordingly, Applicants respectfully submit that the claim amendments are supported by the application as filed and respectfully request entry thereof. Applicants further submit that the claim amendments are not narrowing amendments as the additional language was already inherent in the recitation of a "native" cancer antigen.

II. Rejection under 35 U.S.C. § 103 (a).

Claims 84, 85, 89-93 and 95-102 stand rejected for obviousness over Johnston et al. in view of Falo et al. In the Advisory Action dated August 28, 2001,

the Examiner maintained this rejection on the basis that the presently-claimed compositions would have been obvious to one of ordinary skill in the art at the time of invention.

A. The Olmsted Declaration.

In response to the Declaration of Robert M. Olmsted pursuant to 37 C.F.R. § 1.132 (*hereinafter*, "the Olmsted Declaration"; submitted July 26, 2001), the Examiner stated in the Advisory Action (page 4, lines 7-11):

> Applicant's argument that it would have been unexpected that a composition comprising an alphavirus vector encoding a native cancer antigen could be directly administered to an animal to effectively provide protection against cancer because Falo describes a two-part vaccination strategy is noted; however, its relevance is not completely understood, as applicant's claims are drawn to a composition, not a method.

In a telephone communication subsequent to issuance of the Advisory Action, the Examiner indicated that she would be receptive to arguments as to why the data presented in the Olmsted Declaration are relevant to the patentability of the pending composition claims.

As previously described, the Olmsted Declaration presents data demonstrating the protective effects of an alphavirus replicon vector expressing the HER2/*neu* gene product on the development of mammary tumors in mice. It would have been unexpected from the cited references that direct immunization with an alphavirus vector expressing a native cancer antigen, *i.e.*, an antigen expressed by the cancer of interest, would be effective in providing a protective immune response against cancer. Johnston et al. does not teach the use of alphavirus vectors expressing a native cancer antigen, and Falo et al. teaches a more complicated two-part vaccination strategy with artificial tumor antigens.

In response to the Applicants' previous arguments, the Examiner has questioned whether the suitability of the claimed compositions in an unexpected use or method is sufficient to establish unobviousness of a claimed composition.

Applicants respectfully submit that it is well established in the patent law that "a compound and all of its properties are inseparable; they are one and the same thing." *In re Papesch*, 137 USPQ 43, 51 (C.C.P.A 1963). The Olmsted Declaration indicates that the claimed compositions are more immunogenic and effective in eliciting a response against a native cancer antigen. It is because of these unexpected properties of the claimed compositions that they have novel and unexpected uses (*i.e.*, in methods) as compared with the compounds disclosed in the cited art.

The facts of *In re Papesch*, 137 USPQ 43 (C.C.P.A 1963) are quite similar to those of the instant case, with the exception that *In re Papesch* concerned a pharmaceutical compound rather than a viral vector. A copy of this case is enclosed herewith for the Examiner's convenience. In *In re Papesch*, a claim to a class of compounds was rejected for obviousness on the basis that one species of the claimed class of compounds was structurally obvious over a prior art compound. In response, the Applicant alleged that the claimed compound was unobvious on the basis of unexpected anti-inflammatory properties (*i.e.*, useful in a method of treating inflammation). The Examiner maintained the rejection, stating that the unexpected use of the compound was only relevant to method claims and not compound claims (*In re Papesch* at 44-46).

Specifically, the Examiner stated that:

> The affidavit is interesting but irrelevant to the rejection since it is not directed to the subject matter 'sought to be patented,' namely, the use in the arts of the compounds. The obvious compound is not made less obvious by its properties in an art use. . . . It appears that if an invention is present, it resides in the use of the claimed compounds as anti-inflammatory agents and should be claimed as such.

(*In re Papesch* at 45).

The Board maintained the rejection on the ground that unexpected pharmacological properties were not relevant to the unobviousness of a chemical compound (*In re Papesch* at 47). The Board did not address the question of whether unexpected usefulness of a compound in a new method is sufficient to establish unobviousness of a claimed composition.

The Court of Customs and Patent Appeals reversed the Board, and clearly stated that the reasoning applied by both the Examiner and the Board was erroneous in evaluating the obviousness of a claimed compound. The Court began its opinion with an extensive review of the case law. The Court then asserted that the rejections issued by the Examiner and the Board were contrary to the established case law. Specifically, with respect to the Board's opinion, the Court held that:

> From the standpoint of patent law, a compound and all of its properties are inseparable; they are one and the same thing. . . . And the patentability of the thing does not depend on the similarity of its formula to that of another compound but of the similarity of the former compound to the latter. There is no basis in law for ignoring any property in making such a comparison.

(*In re Papesch* at 51).

With respect to the Examiner's argument that the unexpected uses of the compound were only relevant to <u>method</u> claims, the Court stated:

> As to the examiner's view that in a case such as this the applicant should claim his invention as a process utilizing the newly discovered property, the board appears to have ignored it, properly we think. <u>It is contrary to practically all of the above decisions wherein no fault was found with granting product claims</u>.

(*In re Papesch* at 52; emphasis added). <u>In other words, the Court unambiguously rejected the Examiner's argument that "[t]he obvious compound is not made less obvious by its properties in an art use</u>." (*In re Papesch* at 45).

It is apparent that the facts of the present case are quite similar to those in *In re Papesch*. In the present case, the claimed compounds are unexpectedly potent anti-cancer agents and are unexpectedly advantageous as compared with the compositions in the cited art for treating cancer. As made clear by the holding of *In re Papesch*, both the properties and new uses of the claimed composition are relevant to determining whether the compound possesses unexpected properties and, ultimately, the question of unobviousness. Accordingly, in view of *In re Papesch*, Applicants submit that the unexpectedly potent anti-cancer properties of the claimed compositions and their usefulness in novel methods of treating cancer, as demonstrated by the Olmsted Declaration, are relevant to determining the patentability of the presently-claimed compositions.

Accordingly, for the reasons set forth above, Applicants respectfully submit that the presently claimed compounds are unobvious, and request withdrawal of the outstanding rejection under § 103.

B. The References cannot be Combined to Achieve the Claimed Invention.

In addition to the points addressed above, Applicants maintain that even if the cited Johnston et al. and Falo et al. references are properly combined, the combination does not render the presently-claimed invention obvious. On this point, the Advisory Action states:

> Applicant's disclosure teaches a native cancer antigen as a 'naturally occurring' cancer antigen and as any cancer antigen that is expressed on the surface of a cancer cell. Applicant recites specific embodiments of native cancer antigens as *HER2*, MAGE-1, and MAGE-3, among others. Falo teaches the very same antigens as tumor rejection antigens or as "artificial" target antigens. Thus, absent some evidence to the contrary the "artificial" cancer antigens disclosed by Falo are identical to the "native" cancer antigens of applicant's disclosure. Applicant's assertion that Falo "is intending to use these 'tumor rejection antigens' as artificial tumor antigens, presumably to produce an immune response against that do not

> express these antigens" is noted; however, the examiner can find no such teaching in Falo.

(Advisory Action, paragraph spanning pages 3-4).

Applicants address these points below. As an initial matter, the only *reasonable* interpretation of Falo et al. is that Falo et al. are using the tumor rejection antigens as artificial cancer antigens for cancers that do not normally express these antigens. While Falo et al. is not explicit on this point, clearly this is the most reasonable interpretation to one of ordinary skill in the art. It would make no sense to use the term "artificial" tumor antigen to characterize a tumor antigen that naturally occurs in the cancer cell. Moreover, Falo et al. state that:

> Although some tumor antigens are known, it is currently not feasible to identify relevant tumor antigens for each specific tumor and for each specific patient. The present invention obviates the requirement of having to characterize, isolate and introduce a specific tumor antigen in order to stimulate antigen specific CTL production and subsequent description of affected cells such as neoplastic cells and virally infected cells.

(Falo et al., page 6, lines 2-7). Accordingly, Applicants submit that Falo et al. discloses administration of particular tumor rejection antigens as artificial cancer antigens, for use in cells that do not normally express these antigens.

In contrast, the claimed compositions may unexpectedly be used to induce an immune response against cancer cells that normally express the antigen. Independent Claims 84 and 95 have been amended to recite "said composition effective to treat a cancer cell expressing said native cancer antigen" to more specifically point out this aspect of the invention.

In a telephone conversation with the Examiner, the Examiner expressed concern that an "intended use" limitation was not sufficient to distinguish the claimed composition from the cited art compositions. Applicants agree that an intended use limitation is insufficient in the case of a lack of novelty rejection

under §102. However, Applicants assert that in the case of an obviousness rejection under § 103 an intended use limitation has patentable weight.

In particular, in the present case, the use of an alphavirus vector encoding a native cancer antigen to produce a protective immune response against a cancer cell expressing the antigen (as discussed above and in the Olmsted Declaration) is clearly unexpected and unobvious over the cited Johnston et al. and Falo et al. references.

Finally, the Applicants assert that there would have been no motivation to make the claimed compositions. Indeed, Falo et al. teaches against the use of an alphavirus vector expressing a native cancer antigen to immunize a subject against cancer. As discussed above, Falo et al. teaches a more complex two-part approach to immunizing a subject because a direct vaccination approach would not be effective.

Moreover, neither Falo et al. nor. Johnston et al., alone or in combination, provide the requisite motivation to produce an alphavirus vector encoding a native cancer antigen. The Examiner appears to be arguing that an alphavirus vector encoding a tumor rejection antigen (for use as an artificial tumor antigen, according to Falo et al.) could be used to produce the *in vitro* genetically modified cells of Falo et al. However, the fact that this particular combination of features **could** have been made is irrelevant to the obviousness inquiry. The test for obviousness is whether the references **motivate** the ordinarily skilled worker to make the **particular** combination. Clearly, no such motivation can be found in either of the references, taken alone or in combination. The mere fact that references can be combined does not render the combination obvious unless the prior art also suggests the **desirability** of the combination. *In re Fritch*, 23 USPQ 2d 1780 (CAFC 1992). The Court of Appeals for the Federal Circuit has addressed this issue and has stated that "[t]he mere fact that the prior art could be so modified would not have made the modification obvious **unless the prior art suggested the desirability of the modification**." *In re Gordon*, 221 USPQ, 1125, 1127 (Fed. Cir. 1985) (emphasis added). Clearly, such motivation is absent from the presently-cited references.

After application of the relevant legal standards to the facts of the present case, it is apparent that the claimed compositions are not rendered obvious by the disclosures of Johnston et al. and Falo et al.

In view of the foregoing discussion, Applicants respectfully request that the outstanding obviousness rejection over Johnston et al. and Falo et al. be withdrawn.

III. Conclusion.

The points and concerns raised by the Examiner in the Final Action and Advisory Action having been addressed in full, it is respectfully submitted that this application is in condition for allowance, which action is respectfully requested.

Respectfully submitted,

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Enclosure: *In re Papesch*

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Traci A. Brown
Date of Signature: September 28, 2001

Claim Amendments With Revisions Shown

84. (Twice Amended) A composition comprising infectious alphavirus particles in an immunogenically effective amount, wherein said alphavirus particles comprise one or more heterologous nucleotide sequences encoding an antigen; and wherein said antigen is a native cancer cell antigen, and further wherein said alphavirus particles comprise one or more attenuating mutations, said composition effective to treat a cancer cell expressing said native cancer antigen.

95. (Amended) A composition comprising infectious Venezuelan Equine Encephalitis (VEE) particles in an immunogenically effective amount, wherein said VEE particles comprise one or more heterologous nucleotide sequences encoding an antigen; and wherein said antigen is a native cancer cell antigen, and further wherein said VEE particles comprise one or more attenuating mutations, said composition effective to treat a cancer cell expressing said native cancer antigen.

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